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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/629,074	CRYSTAL ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17-23 and 25-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22,23,25 and 27-33* is/are allowed.

6)☒ Claim(s) *1-12,17-21,26 and 34-43* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed December 23, 2002 (Paper No. 15) has been entered. Claims 4, 21, 26, and 27 have been amended. Claims 28-43 have been newly added.

Accordingly, Claims 1-12, 17-23, and 25-43 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 17-21, and 26 stand rejected and Claims 34-43 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 13 (mailed 8/21/02), because the specification, while being enabling for administering either 1) an adenoviral vector encoding VEGF operably linked to a promoter or 2) an adenoviral vector encoding VEGF and a second osteogenic protein each of which is operably linked to a promoter, to a bone or within a tissue immediately surrounding the bone, whereby bone density or formation is enhanced, does not reasonably provide enablement for administering any type of vector encoding VEGF (and optionally further administering any type of vector encoding an osteogenic protein) to a cell associated with a region of a bone, whereby bone density or formation is enhanced, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-12, 17, and 18 are directed to a method for enhancing bone density or formation by administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding a vascular endothelial growth factor (VEGF), such that the first nucleic acid is expressed in the cell to produce the VEGF, whereby bone density or formation is enhanced within the region, wherein the first cell is within the bone or within a tissue immediately surrounding the bone. Claims 19-21 and 26 are directed to a viral vector comprising at least one first nucleic acid encoding a VEGF and at least one second nucleic acid encoding at least one osteogenic protein.

The arguments advanced on pages 5-8 of the Office Action of Paper No. 5 (mailed 4/24/01), on pages 4-6 of the Office Action of Paper No. 7 (mailed 11/23/01), and on pages 3-4 of the Office Action of Paper No. 11 (mailed 6/5/02) are incorporated herein.

At page 3, paragraph 9 of the response, Applicants argue that when considered in light of the art as a whole, the specification adequately teaches those of skill in the art how to use vector systems other than adenoviral vector systems. Applicants point to the specification at pages 5-6 and the publications cited there for teaching several vector systems that can be employed. Applicants assert that when read in light of the art as a whole, the specification adequately teaches those of skill in the art to use vectors other than adenoviral vectors. However, the Office Action of Paper No. 13 (mailed 8/21/02) cites numerous references pointing to technical barriers in the gene therapy art, particularly with regard to targeting strategies. Applicants have not addressed these issues or provided teachings within the specification with regard to overcoming these technical barriers. The disclosure does not offer a solution to the problems recognized in the art, such that a wide variety of vector types, including both viral and non-viral, could be used to enhance bone density or formation. It is well-established that the specification must enable the full scope of the claimed methods and compositions with specific guidance. Here, the specification fails to adequately teach a method for using a VEGF-encoding vector other than an adenoviral vector to

transfer a VEGF to a target cell and express the VEGF gene at a level sufficient to achieve the claimed effect, i.e. enhanced bone density or formation.

In view of the quantity of experimentation necessary to determine appropriate parameters for practicing the claimed method with other vectors to achieve enhanced bone density or formation in immunocompetent animals, and given the limited applicable working examples directed exclusively to the use of adenoviral vectors, the limited guidance in the specification with regard to the implementation and design of other vectors, the broad scope of the claims with regard to the type of vector to be used, and the unpredictability in the gene therapy art, undue experimentation would have been required for one skilled in the art to practice the claimed method over the full scope and use the claimed compositions over the full scope.

At page 4, paragraph 2 of the response, Applicants refer to the scope of enablement acknowledged by the Examiner and conclude that Claims 34 and 35 should be allowable. However, these claims continue to cover the use of vectors other than adenoviral vectors. For example, although Claim 35 requires that the second nucleic acid is administered via an adenoviral vector, there is no requirement that the first nucleic acid is administered via an adenoviral vector. The claim covers the use of any type of vector for delivery of the first nucleic acid encoding a VEGF.

Conclusion

Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 22, 23, 25, and 27-33 are allowable. Claims 22, 23, 25, and 27-33 are directed to a bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding a VEGF

and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein. The claims are free of the prior art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER